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Establishing a Core Outcome Measure for Graft Health: a Standardized Outcomes in Nephrology – Kidney Transplantation (SONG-Tx) Consensus Workshop Report

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CSH participated in the research design, data collection, data analysis, and provided intellectual input on the manuscript and contributed to manuscript writing.

MAJ participated in the research design, data collection, data analysis, and provided intellectual input on the manuscript and contributed to manuscript writing.

GK participated in the research design, data collection, data analysis, and provided intellectual input on the manuscript and contributed to manuscript writing.

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Abbreviations:

Standardized Outcomes in Nephrology (SONG)

Abstract

Background: Graft loss, a critically important outcome for transplant recipients, is variably defined and measured, and incompletely reported in trials. We convened a consensus workshop on establishing a core outcome measure for graft loss for all trials in kidney transplantation.

Methods: Twenty-five kidney transplant recipients/caregivers and 33 health professionals from eight countries participated. Transcripts were analyzed thematically.

Results: Five themes were identified. "*Graft loss as a continuum"* conceptualizes graft loss as a process, but requiring an endpoint defined as a discrete event. In "*defining an event with precision and accuracy,"* loss of graft function requiring chronic dialysis (minimum 90 days) provided an objective and practical definition; re-transplant would capture pre-emptive transplantation; relisting was readily measured but would overestimate graft loss; and allograft nephrectomy was redundant in being preceded by dialysis. However, the thresholds for renal replacement therapy varied. Conservative management was regarded as too ambiguous and complex to use routinely. "*Distinguishing death-censored graft loss"* would ensure clarity and meaningfulness in interpreting results. "*Consistent reporting for decision-making"* by specifying time points and metrics (i.e. time to event) was suggested. "*Ease of ascertainment and data collection"* of the outcome from registries could support use of registry data to efficiently extend follow-up of trial participants.

Conclusions: A practical and meaningful core outcome measure for graft loss may be defined as chronic dialysis or re-transplant, and distinguished from loss due to death. Consistent reporting of graft loss using standardized metrics and time points may improve the contribution of trials to decision-making in kidney transplantation.

Introduction

Advances in kidney transplantation have yielded remarkable improvements in short-term graft survival. In most high-income countries, more than 95% of recipients have a functioning graft at one year post-transplant[1-3]. However, the rates of graft survival decline to 50-70% after 10 years[4-6], and 20-30% after 20 years[7,8]. Limited improvements in long-term outcomes have been achieved and there have been calls to reform trial design in transplantation[9]. Losing a graft is a critical outcome for patients with a kidney transplant and their clinicians. Many recipients regard this as the most important outcome, even above mortality, as they fear the return to dialysis[10,11]. Yet, many trials conducted in kidney transplantation do not report graft loss at a time point that is meaningful to patients[12-17]. Moreover, graft loss is variably defined, measured and sometimes not even reported in trials[18].

Systematic reviews of trials in kidney transplant recipients consistently show that graft loss is reported using different definitions (return to chronic dialysis, allograft nephrectomy, re-transplant), metrics (such as proportion or time to event), and do not consistently report death-censored graft loss[17,19,20]. Collectively, these problems limit the value of trials in supporting decision-making, make cross trial comparisons problematic, and ultimately impede progress in achieving better long-term graft outcomes.

Recently, the Standardized Outcomes in Nephrology – Kidney Transplantation (SONG-Tx) initiative established six consensus-based core outcomes of critical importance to all stakeholders: graft health, mortality, cardiovascular disease, infection, cancer, and life participation[11,21,22]. Core outcomes are intended to ensure consistent reporting of data from clinical trials and do not necessarily have to be selected as the primary outcome for the trial. Graft health was composed of four graft-related outcome domains: graft loss, acute graft rejection, chronic graft rejection and graft function[22]; with graft loss identified by all stakeholders as the most important to report in trials [11,22].

The emphasis of this workshop is on establishing a consensus-based definition for graft loss and not all graft-related outcomes. This workshop report aims to describe the perspectives of patients, caregivers, and health professionals on establishing a core outcome measure for graft loss, including the definition and metric, to be used in all trials conducted in kidney transplant recipients.

Context and scope

The SONG-Tx Graft Health consensus workshop was convened in Chicago May 1st 2017 during the American Transplant Congress. Consensus workshop is one step in establishing core outcome measure[23], by bringing together the insights from experts to enable decisions to be made. Participants were asked to discuss and provide specific input on establishing a core outcome measure for graft loss – including the definition and metric to measure graft loss in all trials in kidney transplantation. Graft loss was identified as a core outcome to be reported in all trials in kidney transplantation based on consensus among patients, caregivers, and health professionals. Ensuring that trials report critically important outcomes (i.e. graft loss) in a consistent way enables reliable assessment of the comparative effect of interventions across trials, and ultimately improves the relevance, reliability, and efficiency of trials to support treatment decision-making[21,22]. The core outcome does not preclude individual triallists from using additional outcomes measures that are of specific relevance to the trial. Core outcome sets are a set of outcomes that should be reported as a minimum in clinical trials for a specific clinical area, however they do not necessarily have to be used as the primary endpoint of the trial.

To prompt the discussion, we presented a preliminary definition for graft loss based on definitions that have been used in trials in kidney transplantation: “need for kidney replacement therapy (chronic dialysis for more than 90 days, repeat kidney transplant, conservative management)”; and examples of metrics (time to event, proportion with a functioning graft at a given time point). We

clarified that graft loss would be addressed separate from mortality (i.e. death with a functioning graft).

Attendees and contributors

Fifty-eight stakeholders attended the workshop; 16 (28%) were patients with a kidney transplant, 9 (15%) were caregivers, and 33 (57%) were health professionals including nephrologists, surgeons, psychiatrists, psychologists, nurses, researchers, policy makers, and industry representatives. The attendees were from eight countries including Australia, Austria, Canada, France, Norway, United Kingdom, United States, and Vietnam. We identified "key informant" health professionals with clinical experience in kidney transplantation, and/or with interest and expertise in research focussed on graft outcomes. We also invited health professionals with an advisory or leadership role in relevant professional societies (including the American Society of Transplantation (AST), The Transplantation Society (TTS), Canadian Society of Transplantation (CST), Transplantation Society of Australia and New Zealand (TSANZ)), regulatory and agencies (including the Food and Drug Administration (FDA), United Network for Organ Sharing (UNOS)), funding organizations (National Institutes of Health (NIH)), and registries (including the Scientific Registry of Transplant Recipients (SRTR), UK Renal Registry, Australian and New Zealand Dialysis and Transplantation Registry (ANZDATA)). Patients and caregivers who resided in the United States were invited by local SONG-Tx Graft Health workshop investigators, and received reimbursement for parking and ground transportation. All contributors who were unable to attend the workshop received a copy of the workshop program, materials and draft report to provide feedback and comment (Supplemental File 1).

Workshop program and break out discussions

All contributors and attendees received the workshop program and background materials two weeks prior to the workshop. To maximize diverse discussion and broad knowledge exchange among different stakeholders, all participants were pre-assigned to one of six break out discussion groups comprising a mix of patients/caregivers and health professionals. After a short presentation on the SONG-Tx initiative and current measures for graft health, the breakout discussions commenced. Each group had a facilitator who prompted the discussion using a question guide developed in planning calls with the SONG-Tx Graft Health Expert Working Group (Supplemental File 2). Participants were asked to provide feedback and suggestions regarding the definition of graft loss to be measured in clinical trials (including definition, and metric), and other considerations in selecting or developing the core outcome measure for graft loss. The groups reconvened to provide a brief summary in the final plenary session, which was moderated by the workshop Chair (G.K.). At the conclusion of the workshop, the Chair (G.K.) summarized the key points presented across all groups.

The plenary and break out discussions were audio-taped and transcribed verbatim. All transcripts were imported into HyperRESEARCH software for qualitative data management. First author (A.T.) read and coded the transcripts line by line to identify themes related to establishing a core outcome measures for graft health. A draft workshop report containing a description of the themes was sent to all participants and contributors (including those who did not attend) who were invited to provide feedback. Comments provided within a two-week time frame were integrated into the final report.

SYNTHESIS OF WORKSHOP DISCUSSION

We identified five themes that reflected the diversity and perspectives on establishing a core outcome measure for graft loss: graft loss as a continuum; defining an event with precision and accuracy (loss of graft function requiring chronic dialysis was accepted as a practical definition,

distilling the relevance of re-transplant, re-listing, and allograft nephrectomy, variability in thresholds for renal replacement therapy, ambiguity of conservative management); distinguishing death-censored graft loss; consistent reporting for decision-making; and ease of ascertainment and data collection. Selected quotations for each theme are provided in Table 1. Table 2 presents a summary of the recommendations that arose from the consensus workshop.

Graft loss as a continuum

Graft loss was conceptualized by health professionals as a "continuum" whereby "the graft may be failing but the patient does not need to be on dialysis." Some defined this as "graft health, because graft loss is not usually something that is immediate, it is sometimes a projection." The trajectory from chronic kidney disease (CKD) to graft loss was not perceptibly different – "where does CKD and failing, before you are on dialysis, where does that come in?" However, participants agreed that in the context of trials, graft loss needed to be defined as a discrete event for pragmatic reasons including standardization.

Defining an event with precision and accuracy

Chronic dialysis as a practical definition

Health professionals agreed that graft loss could be defined as requiring chronic dialysis for more than 90 days as this was a "straightforward," "clear," and "precisely defined" measure, a discrete event for which the date could be easily recorded. Although the time frame of 90 days was recognized as "arbitrary," chronic dialysis could be used to distinguish "acute or short-lived [graft failure] versus the longer chronic ones," and served as a reasonable "database" or "regulatory" definition. However, health professionals acknowledged the "gaps in the definition". The chances of recovering graft function during this time frame was possible, although such occurrences were

noted to be rare. Some remarked that the risk of mortality was high during this three-month period, and were uncertain about classifying this as graft failure or death. They also identified the need to ensure that the "data lock date" did not prevent a trial participant who recommenced dialysis thirty days prior to data lock from being recorded as graft loss. For example, a trial investigator may be certain that the graft has been lost on clinical grounds and started the patient on chronic dialysis, yet the clinical research associate (or trial monitor) may insist that this cannot be recorded as a true "graft loss" as the patient had not been on dialysis for 90 days. Thus, it was suggested that the definition could be expanded to include "dialysis commenced for the long-term in the estimation of the caring clinician." From the patients' perspective, dialysis signified graft loss – "as a patient, I look at going on dialysis as a failure, period, a real switch point in your minds saying, 'ok I guess the graft has failed'."

Distilling the relevance of re-transplant, re-listing, and allograft nephrectomy

Re-transplant was also considered a clear and clinically important event that was important to include in the definition as patients could be pre-emptively re-transplanted without return to chronic dialysis. In particular, this would be relevant in countries where a living donor kidney transplant could be performed prior to listing, including in countries without robust deceased donor kidney transplant systems. However, one clinician argued, "I would favor re-listing as opposed to re-transplantation because sadly, there will be many patients that reach a point of re-listing and they may well die waiting and those should be considered graft losses not death with a functioning graft, even if they are eking [to endure] it out with the barest minimum of kidney function."

Re-listing a patient on the transplant waiting list could be considered as graft loss, and was recognized by health professionals as a "key decision" that could be readily recorded. For some patients, being re-listed signified graft loss:

"If your doctor came up and said your kidney's down to less than 20%, I'm going to put you on the transplant list, now you're not on dialysis, would you feel that your transplant is failing?" (clinician)

"… Yes, as a matter of fact it happened. Before my numbers got low enough, I was confronted with another cadaveric kidney transplant." (patient)

In contrast, some health professionals reasoned that re-listing "did not make sense and was more arbitrary than starting dialysis" and could occur when the GFR was 20 ml/min/1.73m^2 and patients could still live reasonably well for many years. Many kidney transplant recipients could be placed on the waiting list for several months without requiring dialysis. Therefore, using re-listing as a measure may overestimate graft loss. Some patients/caregivers also commented that re-listing wasn't "necessarily a failure" because patients were being re-listed with "higher GFRs".

Some health professionals argued that transplant nephrectomy was a clearly defined event that could be included in the definition of graft loss; however others stated that this could be confusing as "only a small proportion of patients who lose their graft have a transplant nephrectomy." Also, allograft nephrectomy would be "associated with the need for renal replacement therapy" and was therefore "redundant."

Variability in thresholds for renal replacement therapy

The variability in thresholds for intervention with replacement therapy was identified by clinicians as a challenge to defining graft loss consistently. Timing of chronic dialysis initiation was described as a "moving target" that changed over time – "we used to start people on dialysis closer to [a GFR] of 20 [ml/min/1.73m^2], but now it's getting into the single digits." Some clinicians reflected that "we're very bad at managing chronic graft dysfunction and failure, so we're very late to prepare for

dialysis." However, other clinicians observed that some patients were being re-listed earlier "when they may be at [a GFR of] 15 or 20, when they haven't lost a graft at that point"; and in some countries (such as Norway, which has pre-emptive repeat transplant policies), patients with declining GFRs were monitored closely to be re-listed with higher GFRs of 20 ml/min/1.73m^2. In contrast, clinicians raised concerns about the disparities in re-listing and re-transplant among patients from ethnic minority groups or different socio-economic status who had "different reasons for why transplants fail, people not taking their medications, they're not going to get re-listed so you are waiting for them to go to zero, but for some you wait to go to 20…"

Ambiguity of conservative management

While health professionals recognized that some patients may choose to forgo renal replacement therapy should their graft fail, adding conservative management in the definition of graft loss was regarded as too imprecise, ambiguous, and complex as it was difficult to determine an exact metric or date. Some suggested that including conservative management would allow for a more comprehensive definition of graft loss, and could be recorded as the date of the patients' decision to decline dialysis or re-transplant. However, many contended that conservative management was "quandary from a physician perspective" as patients could change their mind about treatment, and that the decision could be made whilst the patient still had a functioning graft and thus would "create a huge bias by misclassifying [graft loss]." Some patients suggested that conservative management could be included to "educate and empower patients" by making patients aware of the option. Whilst clinicians agreed that conservative management should be included in communication with patients, they explained that conservative management was difficult to measure in the context of a clinical trial.

To account for patients with graft loss who did not commence dialysis or were not relisted/re-transplanted but died due to graft failure, it was suggested that death due to end-stage kidney

disease may be considered in defining graft loss (i.e. based on GFR). However, health professionals identified problems with this definition. For example, patients "may have low levels of GFR and may subsequently be admitted to hospital with pneumonia, chronic heart failure, or something else, deteriorate and may die, then death may be attributed to "pneumonia" or "sepsis" rather than end-stage kidney disease. Also, they reasoned that theoretically, the graft still "functions" until the time of death, irrespective of the cause of death. Separating all-cause mortality from graft loss, and defining graft loss as the need for chronic dialysis and repeat kidney transplant would be "very objective, reproducible, and easy to track in registries."

Distinguishing death-censored graft loss

There was consensus among health professionals to report "death as a separate outcome" and "differentiate graft loss due to death." Some remarked that registries, for example in the United States, currently recorded death as graft loss. The UK registry used three definitions: graft survival (censored for death), patient survival, and transplant survival (where death is not censored). Also, trials typically reported death with a functioning graft to be graft loss. Death-censored graft loss was regarded as a meaningful outcome that should be presented explicitly in a trial. Death-censored graft loss was "interpreted as a new loss of the kidney, the kidney lost to rejection or some other causes; a different way of assessing newer drugs for example, as opposed to death. Both are meaningful. If you can save kidneys with the drugs but you lose the patient, that's not very good." Patients confirmed that, "For graft failure, I think less of death, I think of the kidney failing."

Consistent reporting for decision-making

Participants emphasized the need for consistent reporting of graft loss to support decision-making. One patient remarked, "in all these trials, you have recorded it one way, and you reported it in a different way, it's hard for a doctor to talk to a patient because everybody is saying something

different, if you would make it more universal, then it would be easy for us to make an informed decision." Health professionals specifically recommended that "dates were critical" and suggested to pre-specify time points – "capture it [graft loss] at least on an annual basis beyond one year." Some suggested that it would be easy to assess the proportion of patients with graft loss at specific time points (e.g. at five years), and also that "time to event was a pretty standard way of analyzing it, and more flexible than a defined point of time." Time to event could be readily interpreted, and would also decrease the tendency to have trials that were short in duration. Moreover, health professionals advocated that trials needed to "build into the study longer follow up, to get more people to contribute to the information for that assessment."

Ease of data collection and ascertainment

Another key consideration identified by health professionals was ease in collecting the data including ascertainment in terms of "data source, or patient-reported, provider report, registry report," of which all would require "hard outcomes." The existing capture of dialysis initiation, re-listing and re-transplant in many national registries provides an opportunity to use registry data for longer-term follow-up of trial participants through data integration with minimal additional cost or complexity. To facilitate data linkage with registries, this may require discussion with national authorities who regulate what data are collected for the ESKD population and processes for data access.

DISCUSSION

In the context of a clinical trial, graft loss needs to be defined as a precise and discrete event. Chronic dialysis (for more than 90 days) provides a practical and meaningful definition for graft loss. From the perspective of health professionals, this definition is clinically meaningful and easily recorded as an event; from the perspective of patients, dialysis signifies failure of the graft. Re-

transplant is required in the definition as patients could be pre-emptively transplanted. The other definitions considered including re-listing, allograft nephrectomy, conservative management, and death due to end-stage kidney disease, are more ambiguous and contentious. Health professionals acknowledge that some inconsistency in defining graft loss is inevitable because of the global variability in thresholds for dialysis initiation or re-listing. Re-listing could occur when a patient had a GFR as high as 20 ml/min/1.73m^2, and thus would overestimate graft loss and it would not be precise enough as an event to be used in the context of a trial. Death due to graft loss (or end-stage kidney disease) was suggested; however it was too difficult to make this measure objective and reproducible. Patients, caregivers and health professionals emphasize the need for trials to report death-censored graft loss, in addition to but distinctly different from death, so they could interpret the results in a more meaningful way. Patients reiterated that they did not perceive death as graft loss.

Other initiatives to standardize the definition of graft loss exist. The global Clinical Data Interchange Standards Consortium (CDISC) classifies graft loss as loss of a previously functioning graft or loss due to primary non-function (of which both may require dialysis, re-transplantation, or surgical removal of graft), and graft loss due to death[24]. They state that "dialysis is often presumed to be irreversible after 90 days."[24] Of note, relisting for kidney transplantation was not explicitly included in the definition. As identified during our workshop, this may be because patients can be re-listed with sufficient graft function without significant physical or mental impairment; and thus cannot be used to define graft loss. The European Medicines Agency 2008 Guideline on Clinical Investigation of Immunosuppressants for Solid Organ Transplantation advises the use of clear-cut and discrete criteria for graft loss "such as permanent return to pre-transplantation treatment modality for a defined period of time e.g., return to dialysis for at least 4–6 weeks or more, renal re-transplantation, nephrectomy in kidney transplantation."[25] The U.S. FDA recommends that "the diagnosis of primary nonfunction generally does not become established before 2 to 3 months (90 days) after transplantation[26]. As previously noted, the SONG-Tx core outcomes are established to

ensure that there is consistent reported of data across clinical trials in transplantation and do not have to be used as the primary outcome to determine sample size of the trial.

There is broad consensus among all stakeholders that graft loss is a critically important outcome to be reported in trials[11,22]. However, trials in kidney transplantation are typically short in duration[12-14] and therefore unlikely to demonstrate a difference in the effect of an intervention on graft loss. There are now increasing calls for trials to conduct longer-follow up. The existing capture of dialysis initiation, re-transplant, and re-listing in many national registries provides an opportunity for data integration strategies to extend the follow-up of trial participants with minimal added cost or complexity[27]. As emphasized by the workshop participants and contributors, the ease of data collection and ascertainment are necessary to support implementation of a core outcome measure for graft loss – including in registries.

The recommendations for establishing a core outcome measure for graft loss shown in Table 2 are based on the collective input from patients, caregivers, and health professionals. We acknowledge that the majority of participants were from high-income, English-speaking countries and patients were recruited from Chicago because of feasibility. However, we elicited input from participants in low-income countries and the discussion and the recommendations that arose from the workshop appear to be internationally applicable and relevant. This workshop focussed on developing a core outcome measure for graft loss.

More broadly, we acknowledge other efforts to define endpoints related to graft health. The U.S. FDA has developed guidance on surrogate endpoints in kidney transplantation including delayed graft function[26], and in the past year convened workshops to address surrogate endpoints for clinical trials in kidney transplantation[28], and antibody-mediated rejection[29]. Another example is the ongoing work by the Banff initiative since 1991 in developing the classification of renal allograft biopsies, which integrates histologic, serologic, and molecular diagnostic techniques to produce a

consensus-based reporting system for graft rejection[30-32]. However, there is no accepted or FDA-approved surrogate endpoint for graft loss[9].

The workshop recommendations will directly inform the proposal of a core outcome measure for graft loss that will be piloted prior to broader implementation in trials, and with the growing interest in registry-based trials, potentially also in registries. Further detailed and technical work on the measurement and analysis of graft loss will be undertaken. Establishing and implementing a core outcome measure for graft loss in all trials in kidney transplant is likely to improve consistency in trial reporting, and thereby strengthen the evidence-base for shared decision-making to improve the care and outcomes of kidney transplant recipients.

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Table 1. Quotations to support each theme

Themes and illustrative quotations
Graft loss as a continuum
From the physician standpoint, in a way it's a continuum, the graft maybe failing but they don't need to be on dialysis, sometimes we can just keep the transplant going for a long time. So graft loss, is basically, it stops working, and you go back on dialysis. H5
When I have a lot of patients with failing grafts, before they get on dialysis, they're sometimes really miserable, on phosphate binders and doing well and they're tired…. where does CKD, where does CKD and failing, before you are on dialysis, where does that come in? H5
When I think of graft loss, I think of graft health, because graft loss is usually not something that is immediate, it's sometimes a projection just as we all age, things will slowly get better or worse. H6
Defining an event with precision and accuracy
Chronic dialysis as a practical definition
The 90 days in the US, after 12 weeks of lets, say acute renal failure and being on dialysis, chances of recovering kidney function sufficient enough to be off dialysis are low so that's why, we fill out the form, end-stage kidney disease, we wait that time, in fact this is also the highest period when the patients are at high risk for dying so, first three months, who survives the three months. H4
From the patient perspective, needing dialysis is a negative thing…from the scientific perspective, it's either being on dialysis, and or reaching the point of needing a kidney. H4
It's clear cut, if you have dialysis for 3 months, that's reasonable, the only problem with the three months thing is that some people will have as you mention irrecoverable renal function and die at 6 weeks, so what is that, is that graft failure or is that death? H4
We have to make a distinction here between the acute loss versus chronic one, in an acute one, 30 days, the kidney come back, in the chronic one the GFR of 20 but the kidney function goes down slowly, on dialysis because you lost your kidney function gradually or, so patients who are sick and they get on dialysis, most of them come back, so that's why you have to wait for three months. H4
I could see when you have insertion of the peritoneal dialysis catheter or the creation of vascular access, I can see how that would be a real switch point in your minds saying ok I guess its failed, and it's your dialysis, cause we just did something. H4
This is the definition we do in a lot of drug studies that we do…getting on dialysis for 90 days is a regulatory definition and sometimes is used as an endpoint so when you're trying a new drug, measuring whether the drug is better than Drug A, versus what you are on now. If you end up on dialysis and it's called a graft loss, then that drug probably won't get approved so it's a tough definition. H5
I feel sad for the patient who has to go back on dialysis. P6
An issue on the chronic dialysis piece, that 90 day rule is a pretty arbitrary one. Patients could have an illness that causes their kidney to not function well for only a temporary period, and so that they could get dialysis in the meantime, but most times it doesn't last longer than 90 days, they get better and they come off dialysis, that wouldn't really be a graft loss per se, so that 90 day window is trying to sort of tease out the ones that are quote unquote acute or shortlived versus the longer chronic ones, the problem there is that you have to wait until that happens to decide, at the time you don't know which way this person's going to go and once you decide where time zero is, is it the 90 day point or is it the origin at which you do dialysis, from a survival analysis perspective. The bottom line is I think that has to be clarified. But the kidney replacement therapy piece is quite reasonable. H6
Sometimes its just very difficult to distinguish and say for someone with heart problems whose kidneys fail they went on dialysis and they were able to come off but it doesn't mean they were able to achieve the same level of function as they did before because the heart was so sick, the heart disease, it may have had a role to play in changing the level of kidney function as you now resume with afterwards so it has its own impact so to speak. So that's where I think, reading this, if we're talking about graft loss, that is one area I'm wondering how we are going to address, it has come up in trials. H6
Distilling relevance of re-transplant, re-listing, and allograft nephrectomy
On the list of things that are included in the graft loss definition, nephrectomy is not there, which seems like an oversight, nephrectomy is clear. H2
One thing was that whether allograft nephrectomy should be included but that would really be associated with the need for renal replacement therapy so I suppose that would be redundant. H3
I don't think that transplant nephrectomy should be included, categorised in trials, because only a small proportion of patients who lose their graft have a transplant nephrectomy so its confusing. H4
Before my numbers got low enough I was confronted with another cadaveric kidney transplant so I was one of the people that never actually went back on dialysis, thank god cause it's a horrible life, the diet, the restrictions, its nasty, and so that's failure, just like you were saying, that's failure, so that's graft loss. P4
Re-listing is not necessarily a failure, my wife an example of that, she never went through dialysis, and couldn't go through dialysis so just the fact that she relisted wouldn't necessarily be a failure, and it was pointed out that more and more people are going on the wait list with higher GFRs like in that 15 to 20 range so that sort of is a major factor considered in that may not have existed years ago. (Plenary)
Variability of thresholds for renal replacement therapy
It is a bit of a moving target though I mean we used to start people on dialysis closer to [a GFR of] 20 but now it's like getting

into the single digits. H1

I was just thinking what the definition was, the start of dialysis which is basically the very same one, if you want to have a non, precise definition, if you're a patient treated in the profit unit, the provider might suggest you have a GFR of 15, that's not sufficient and you start dialysis. H2

Things are changing. We're very bad at managing chronic graft dysfunction and failure, so we're very late to prepare for dialysis, now that's changing and now we are looking at people with GFRs under 20, native renal disease patients, and in some places they've got separate clinics for the failing graft. I don't think its graft loss at that point, it's a bit like advanced chronic kidney disease. The kidneys haven't totally failed, but we are getting better at preparing people for re-transplantation. We're re-transplanting people earlier when they maybe [a GFR of] 15 or 20, they haven't lost their graft at that point, it could be 6 to 12, 18 months because we are intervening earlier, so how do you allow for that, when we are making that conservative decision earlier as well so that we are better at giving EPO. H4

This has moved a bit, I don't think we treat these people quite optimally we should be treating these people like the, pre-dialysis clinics that we have or the low clearance clinics, so how do you allow for that? If you categorize everybody. H4

My only concern is that different ethnic groups and different socio-economic status, have different reasons why transplants fail, people not taking their medications, they're not going to get re-listed so you are waiting for them to go to zero, but you wait for some to go to 20. H4

Ambiguity of conservative management

Conservative management part, I'm not sure how you measure that, so someone could say I don't want it now but then when they get sick they might change their mind, it is a bit of a quandary from a physician perspective. H1

Conservative management is a choice, but when it would occur? It's hard, if you're having the discussion, the doctor might say 'I think you need to start dialysis now' and you're saying 'well I don't really want to ever start dialysis.' That's hard to define that as a starting point because you may live weeks to months. H1

It's pretty imprecise, our ability to prognosticate, it's pretty off. H1

That's my only problem with taking it out of there of the definition. The definitions are there to educate and empower patients by telling them all of that, if a patient, they are able to self-educate themselves about what their options are. P1

A more technical issue with conservative management thing is that a lot of trials are moving to save money. Now they're trying to link up to all these other databases that exist in the United States, but there's one in Canada, Australia, European countries, so there would be no measurement of conservative care in these kind of databases. It would add an issue of potentially cost and complexity, it does add to the practically of it, I would just see people not implementing it. H1

If you are getting to that point and having that conversation, the patient chooses not to pursue it that's one thing but really the discrete starting point seems to be the conversation, the identification of failure kidneys and discussion of treatment options and even it its not perfect because it'll be hard to track. H2

There's a huge north south gradient, at least in Europe, there's England or the Nordic countries, they had a lot of patients, in Italy, there's nobody that's ever withdrawn from dialysis. H2

Because if you are thinking about a new therapy, the whole idea of having these endpoints is that we have better clinical trial design, and if the endpoint is your function is so poor, you need renal replacement therapy, you want to be comprehensive to include the conservative management, to me that's a treatment failure. H5

Conservative management is quite non-descript in terms of how you want to capture that in trials, it would be open to interpretation of what that is, and also it's really intent not to pursue dialysis, so that would have to be defined, to make sure that's been applied appropriately. (Plenary)

Distinguishing death censored graft loss

The flip side is if you don't include that then everybody that, the doctor says you either need to start dialysis or re-transplant we don't have something like that and patients say I don't want to do those two, that would never be counted as graft loss, and then you're numbers are off, because they will eventually pass away but they won't be counted as graft loss even though their kidney function was really really bad, you have to include them somehow. H1 …But they would be counted as a death in a trial. H1 …But the graft loss is a separate definition and that would be undercounted. H1

It was a very clear rationale for having death as a separate outcome, for instance the SRTR, which is our national registry, you guys count death as a graft loss. H1 … So nephrologists might say oh that's not fair, there's a car accident, that didn't have anything to do with my kidney care. I've actually had conversations with people, they said well that graft is no longer functioning, that's the definition we're talking about and so I'm curious from this standpoint, I know they are making a very different, they're trying hard to separate that but that's going to conflict with some major other reports. H1

I think less of death, I think of kidney failing. P2

The traditional way of reporting graft loss is death with a functioning graft but then some people also report death censored graft loss, they both have meaning, but in my view is that they, they both ought to be presented, or if you present, death-censored, you have to be clear that it is death censored. H3

Suppose the aim is have death with functioning graft, but to have a prolonged life and not a premature death, so the aim is to keep it working, there's sort of nuances to the data. H3

Graft loss for a clinician is very difficult, it's very depressing for the individual, but we need to differentiate between graft loss due to death which I don't think is graft loss because the graft is often still functioning and in many trials, it's very confusing, and that's something which I think should be clarified. Death should be death, and graft loss shouldn't be included in that. H4

Sadly there will be many patients that reach a point of re-listing and they may well die waiting and those should be considered graft losses not death with a functioning graft even if they are eking it out with the barest minimum of kidney function, that's where I think re-listing captures a very meaningful outcome that failures of the graft. H4

The other thing is death with a functioning graft, because that of course is a graft loss. When we record stats in the UK, we

record transplant survival meaning graft loss with death. H5
You will see the Kaplan-Meier, will have death censored graft loss, and the metric for one year, patient death. H5
Consistent reporting for decision-making
So one would say 6 months after the transplant, the other would say 8% functioning at one year. H3
You also have to talk about the kidney totally failing, and then it has to be universal, like you said all these trials, but you have recorded it one way, you reported it in a different way, it's hard for a doctor to talk to a patient because everybody is saying something different, so if you would make it more universal then it would be easy for us to make an informed decision. P4
The way the data are analysed sometimes isn't lined up with what the intent of the investigator is so there is a bit of a disconnect. In this case I agree dates are critical, do we have to pre-specify, do we have to come to consensus around what time points we report. H6
Grafts can last very long, that's the goal, then you really would have to capture it at least on an annual basis beyond the year. H6
What's at stake here is when you only have five people die in one group and two people die in the other group, in a year, does that provide any meaningful information about for example new treatments affecting people? Probably not. So as a result you would have to build into the study longer follow up, to get more people to contribute to the information for that assessment or more patients, to provide you more data. The other thing to inform this is the biology. So the reasons why kidneys are lost within the first year versus beyond the first year are different. If you are interested in those causes that cause kidney loss in the first year, then naturally you want to study losses in the first year, you can't just study five or two patients, so you need more patients followed over a year. Alternatively, in things that occur after a year then you may be able to follow the hundred patients for longer but then you have to make sure that you achieve the follow up, so it depends on what you are looking at ultimately, H6
Ease of data collection and ascertainment
That would be my worry, they would say 'I know this has been recommended but we're not doing it because we're going to save way more money by this'. H1
Which one is easier to measure, that's what they're looking for. H1
Did that mean ascertainment in terms of data source, or patient reported, provider report, registry report, cause all these different sources have varying levels of, but at the heart of it these, they're good, they're hard outcomes. H3
One of the considerations is the ease in gathering the data, so if everything went into a central registry…the ease with which you can find the data is important, H3
The easiest one to measure, to capture, is the kidney transplant, the hardest one to measure is the conservative management and somewhere in between chronic dialysis depending on how you are going to capture that. H5
Time to event is pretty standard way of analysing it, it's more flexible then a defined point in time. H5

H, health professional, P, patient, C, caregiver/family member, number indicated refers to Group ID (1 – 6)

Table 2. Summary of workshop recommendations for establishing a core outcome measure for graft loss

Implications for establishing a core outcome measure for graft loss

- The core outcome measure for graft loss requires a precise definition.
- Chronic dialysis for more than 90 days should be included in the definition for graft loss as this is precisely defined, clear, and is the current definition used in registries and by regulatory agencies.
- Repeat kidney transplant should be included in the definition for graft loss because some patients may be pre-emptively re-transplanted without return to chronic dialysis.
- Re-listing for kidney transplantation can be readily measured, however patients may be re-listed with relatively good kidney function and thus may overestimate graft loss, and it would not be a precise enough event to be used in the context of a trial.
- It may not be informative to include allograft nephrectomy in the definition for graft loss as this is a rare event and is associated with the need for renal replacement therapy (i.e. chronic dialysis or transplant).
- It would not be feasible to include conservative management in the definition for graft loss because of ambiguity, complexity and inconsistency in the definition, and it would be difficult to determine an exact time of event.
- Death due to end-stage kidney disease would not provide an objective and reproducible measure therefore cannot be included in the definition of graft loss.
- Death (from any cause) should be reported as a separate outcome to graft loss.
- Death-censored graft loss should be reported as this is meaningful to all stakeholders.
- A standard metric should be established i.e. time to event or a consistent time point for measurement (i.e. at least annually) to enable informed decision-making.

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